REMARKS

In accordance with 37 C.F.R. §1.121, a marked up copy of the presently amended specification paragraphs and claims is appended hereto. Additions are noted by underlining and deletions are noted by bracketing. These amendments do not introduce any new matter.

Claims 1-165 were originally filed. After misunderstanding the nature of the Election/Restriction of Paper No. 6, Applicants erroneously cancelled claims 158-160, and 162 in their response. The Examiner then withdrew claims 19, 47, and 161 under 37 CFR 1.142(b). The Examiner also withdrew claims 58-149, 163, and 164. Thus, claims 1-18, 20-46, 48-57, 150-157, and 165 are pending prior to entry of this amendment. After entry of this amendment, claims 1-18, 20-46, 48 - 149, 150-153, 155-157, 163-165, and 166-173 are pending.

Claims 19, 47 and 154 are herein cancelled. The amendments to claims 1, 58, 70, 75, 84, 89, 97, 106, 107, 109, 110, 112, 121, 126, 138, 150, 161, 163, and 164 limit the scope of the claims to Group I, identified by the Examiner in paper 6, dated June 18, 2001. Amendments to claims 2, 3, 48, 50, 64, 81, 83, 84, 89, 93, 109, 110, 112, 118, 124, 131, 141, and 151 are not related to patentability, nor do they narrow the scope of the originally filed claims. Rather, these amendments are supported by the specification and are being made merely to correct typographical and clerical errors. Claims 38, 42, 46, 101, 108, 115, 150, 163, 164 and 165 have been amended to rephrase the invention, by substituting "compound" in place of "prodrug" or substituting "MPO_3^{2-}, $MP_2O_6^{3-}$, $MP_3O_9^{4-}$ or "$MP(O)(NR^6)O^-$" in place of "hyperlipidemia agent" notwithstanding Applicant's belief that the claims would have been allowable as originally filed. The scope of these claims has not been narrowed. Claims 70 and 75 have been rephrased by substitution of "by administering to an animal" in place of "using", notwithstanding Applicant's belief that the claims would have been allowable as originally filed. The scope of these claims has not been narrowed. Claim 89 has been further amended to correct the chemical structure included therein. Such an amendment is supported in the specification at page 39 line 11 to page 40 line 4, further at page 7, line 8 through page 9, line 4. New claim 166 adds no new matter and is supported in the specification in originally filed claim 154 and in the specification at page 9, lines 6 – 9. New claims 167 – 170 add no new matter, but reintroduce claims cancelled in the Response to the Election/Restriction Requirement. Support for these new claims can be found throughout the specification, in particular in originally filed claims 158 – 160 and 162 and in the specification page 9 lines 6 – 14. New claim 171 is directed to compounds susceptible to oxidation according to the

mechanism generally depicted in the scheme on page 33, mechanism (2) and described on page 34, lines 1-4. New claim 172 is directed to compounds susceptible to oxidation according to the mechanism generally depicted in the scheme on page 33, mechanism (3) and described on page 34, lines 1-4. New claim 173 is directed to compounds susceptible to oxidation according to the mechanism generally depicted in the scheme on page 33, mechanism (1) and described on page 34, lines 1-4. New claims 171-173 add no new matter.

Applicants also note that the Request for a Corrected Filing Receipt, mailed on June 28, 2001, has not been acted upon in the subject matter. Action on the same is again requested.

The Restriction Requirement

In Paper No. 6 dated June 18, 2001, the Examiner set forth "Election/Restrictions" with enumerated Groups I-XXII. There were two composition groups, 16 methods of use groups, two methods of making groups, and two intermediate groups. Throughout the Election/Restriction, the Examiner did not use the standard form paragraphs found in the MPEP. The Election/Restrictions requirement apparently was not understood when filing Applicants' last response, nor is it well-understood now. Applicants had thought that Groups III-XVIII (uses of the compounds of Groups I and II) were subject to an election of species between Groups I and II. Applicants did not understand that the paper titled "Election/Restrictions" in fact contained no elections, but rather was a 22-way restriction. Had Applicants understood the implications of the Election/Restrictions requirement set forth in the last Office Action, Applicants would have more explicitly traversed the restriction requirement in its entirety.

In the June 18, 2001 paper, the Examiner never explained why the "use" claims of Groups III-XVIII were separate inventions from each other nor separate inventions from Groups I and II as required by MPEP Section 806.05(h). According to that section of the MPEP, the burden is on the Examiner to provide an example of either how the process as claimed can be practiced with another materially different product or how the product as claimed can be used in a materially different process. Indeed, even in the present Office Action, the Examiner still has not complied with MPEP Section 806.05(h).

The Examiner's citation to Section 806.05(h) for the proposition that "This says a single process, not Applicants' sixteen separate processes" is misplaced. (Quote from Office Action at pp2-3.) That section provides no basis for the Examiner's proposition that multiple processes must be restricted from

the product claims. Indeed, the MPEP does not contain any rule that multiple use claims must be restricted. Paper No. 6 shows that all of the use claims are in the same class and subclass. The Examiner's search on the composition claims will necessarily turn up any art using the same compositions. Thus, it is no burden on the Examiner to include the uses of Groups III-XVIII when examining the compound claims of Group I or II.

The Examiner also argued that "The Utility Guidelines have been changed to require one specific utility consistent with 37 CFR 1.1475 and PCT Rule 13.2." (Office action at p. 3). The Examiner apparently believes that the new utility guidelines have somehow created new restriction guidelines. But they have not. The Utility Guidelines merely require a specific and credible utility. Nowhere do the guidelines state that if the compounds have more than one credible utility, that the use claims must be restricted from the compound claims or from each other. The Examiner's citation to 37 CFR 1.141(a) does not alleviate the Examiner's burden to show distinctness.

Furthermore, according to 37 CFR 1.141(b) "Where claims to all three categories, product, process of making, and process of use, are included in a national application, a three way requirement can only be made where the process of making is distinct from the product." It is apparent that the Examiner admitted that a three way restriction was not proper because he acknowledged Applicants' election of Groups I and XIX, which are product and process of making claims. Thus, the Examiner does not believe that composition claims and the process of making claims are distinct under 806.05(f). Therefore, it is proper to keep the product, process of making and process of use claims together in this application. Just because there are multiple process of making and multiple process of use claims for Group I products does not mean that the Examiner can ignore 37 CFR 1.141(b).

The Examiner's restriction of the intermediates of Groups XXI and XXII also does not make sense as they are intermediates of the final products of Groups I and II. According to MPEP Section 806.04(b) (third paragraph) cited by the Examiner, a "species of carbon compounds may be related to each other as intermediate and final product. Thus, these species are not independent and in order to sustain a restriction requirement, distinctness must be shown. Distinctness is proven if it can be shown that the intermediate product is useful other than to make the final product. Otherwise, the disclosed relationship would preclude their being issued in separate patents." The Examiner has stated that the intermediates find other use in the process claims of Group XIX and XX. But those process claims are directed to the method of making the final products. Furthermore, Groups XXI and XXII are in the

same class and subclass as Groups XIX and XX. As such, there is no undue burden on the Examiner to examine these groups together.

As a whole, the breakdown of the pending claims and their dependencies is as follows:

Claims 1- 18, 20-46, and 47-57, 102- 103, 165, and new claims 171-173 are compounds of Formula I in Group I and all depend ultimately from claim 1;

Claims 58-101, 104-149, 163, and 164 all recite uses of the compounds of Formula I;

Claims 150-157 and 166-169 are directed to methods of synthesizing the compounds of Formula I; and

Claims 161 and 170 are directed to intermediates used to make compounds of Formula I.

First, at least claims 102-103 were improperly included within the group of withdrawn claims. These two claims are ultimately dependent from claim 1, which are being examined on their merits. Thus, rejoinder of claims 102-103 is proper and hereby requested.

Second, as claims 58-101, 104-149, 150-157, 163 - 164 and 166- 169 recite all the limitations of claim 1, a serious burden would not be imposed on the Examiner for examination of those claims as well as those of claims 1-18, 20-46, 47-57, 102-103, 165, and 171-173. In addition claims 161 and 170 share the same class and subclass as claims 150 - 157 and also do not pose a serious burden on the Examiner. As set forth in MPEP §803, a serious burden on the Examiner is required in order for restriction to be proper. As this is not the case in the present application, rejoinder of these claims is respectfully requested.

Finally, Applicants respectfully request that the Examiner reconsider his preliminary determination that there are 22 distinct inventions. Applicants request that the Examiner examine Group I claims, Group I products in Groups III-XVIII (methods of use), Group I products in Groups XIX- XX (method of making), and Group I products in Groups XXI- XXII (intermediates). All of these claims are clearly related by the final product claims of Group I.

The examiner has withdrawn from consideration claims 19, 47, 58-149, 161, 163, and 164. Applicants respectfully request that the withdrawn claims, except 19 and 47, be rejoined and examined on their merits for the foregoing reasons.

The Information Disclosure Statement

The Examiner indicated that a legible copy of each document cited in the Information Disclosure Statement mailed on June 7, 2001 was not received. Applicants submit that, as stated in their Transmittal Letter and Return Postcard, copies of the 46 referenced documents were enclosed with the Information Disclosure Statement (copy of date stamped receipt post card enclosed). However, for the Examiner's convenience, replacement copies of the referenced documents are enclosed herewith with a new PTO-1449 that contains corrections of some clerical errors. Applicants' have also submitted a Supplemental Information Disclosure Statement with copies of references cited. Applicants hereby request that an initialed copy of the PTO-1449 and SB/08A forms submitted with the Information Disclosure Statement and Supplemental Information Disclosure Statement, respectively, be sent to Applicants at the Examiner's earliest convenience.

The Markush Group Rejection

Claims 1-16, 20-46, 48-57, 150-157, and 165 stand rejected by the Patent Office as allegedly being drawn to an improper Markush group. In making the rejection, the Examiner refers to In re Harnisch, 206 USPQ 300 (CCPA 1980) and states: "The claimed compounds, compositions, and methods that employ them present a variable core." The Examiner then states that deleting non-elected subject matter obviates this rejection and suggests deleting any reference to where "both Y = nitrogen."

Applicants have amended the claims to reflect the restriction of Group I compounds from Group II compounds. As such, Applicants respectfully request that the Examiner withdraw this rejection.

The Claim Objection

Claims 152, 155, and 156 stand objected to under 37 C.F.R. §1.75(c) as allegedly being in improper dependent form for failing to further limit the subject matter of a previous claim. In supporting this rejection, the Examiner notes that the independent claim from which claims 152, 155, and 156 ultimately depend, recites a proviso that "V, Z, W, W' are not all –H." The Examiner then concludes that all "molecules containing the fragment Y-CH(V)CH(Z)-CW(W')-Y must be chiral and no subject matter is excluded by the requirement "is chiral." This rejection is respectfully traversed.

The fragment Y-CH(V)CH(Z)-CW(W')-Y is not necessarily always chiral when "V, Z, W and W' are not all –H." For example, within the limits of the referenced proviso, it is possible that V = –H,

Z = –H and W is the same as or different from W', whereby said fragment may be achiral or chiral, respectively. Dependent claim 152, which is drawn to complexes wherein said fragment is chiral, appropriately narrows claim 150 and dependent claims 155 and 156 appropriately narrow claim 166 from which they now ultimately depend. Applicants respectfully request that the objection be withdrawn.

The 35 U.S.C. §112, First Paragraph, Rejections

The First Rejection

Claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-157, and 165 stand rejected under 35 U.S.C. §112, First Paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

Specifically, the Examiner contends that, the phrase in lines 16-17, page 128, "M is selected from . . . but is not an FBPase inhibitor" lacks written description." (Office Action p. 11) The Examiner states,

> Applicants' claims are drawn to any molecule with a specific biological property. What are the structures of these molecules and where in the specification do Applicants teach how to make this potentially limitless structural variety of such molecules? . . . Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise. (Office Action p. 11)

Applicants respectfully submit that the M phrase does not lack written description. First, Applicants are not claiming "any molecule with a specific biological property" as the Examiner claims. Rather, Applicants are only claiming a group cyclic of phosphororamides of Formula I. Only the M moiety is defined based on the biological properties.

In the specification (page 8, lines 26-28), Applicants identify suitable M variables as those that, when attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$, or $P(O)(NHR^6)O^-$, are biologically active agents. The specification further teaches that: "[B]iologically active compounds include, for example, anticancer agents, antiviral agents, and antibiotic agents." (page 15, lines 22-23) Biologically active agent refers to a chemical entity that produces a biological effect, in this case - $M\text{-}PO_3^{2-}$, $M\text{-}P(O\text{-})NHR^{6-}$, $MP_2O_6^{3-}$, or $MP_3O_9^{4-}$, where M can be the same M as in the parent drug or a metabolite. (page 21, line 32, to page 22, line 2)

Furthermore, "FBPase inhibitors" are defined on page 21, lines 27-31, of the specification. Therein, Applicants teach that FBPase inhibitors are "compounds that inhibit the human enzyme fructose 1,6-bisphosphatase with an IC50 of at least 100 μM and lower glucose in a normal 18-hour fasted rat following a 100 mg/kg dose i.v. The biologically active FBPase inhibitors are M-PO_3^{2-} wherein M is connected via a carbon, or via an oxygen when MH is a imidazole containing nucleoside analog." These are standard assays. No undue experimentation is required to determine if M-PO_3^{2-} is an FBPase inhibitor as defined.

Despite the Examiner's contention, it is not possible to use structural formulas, names, or both to describe all of the M groups. Given the breadth of the teaching of the specification, Applicants are entitled to the compounds of Formula I where M is defined in part based on biological function.

Moreover, it should be noted that the rejected claims are included in the originally filed claim set. Section I.A. of the Patent Office's Written Description Guidelines states: "There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." (citing In re Wertheim , 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976)) Further, in Section II.A. of the Written Description Guidelines, the Patent Office directs that "rejection of an original claim for lack of written description should be rare." Despite this direction, the Examiner has rejected the original claims as allegedly lacking written description.

The present specification clearly teaches that Applicants were in possession of the claimed invention as a whole at the time the application was filed. The Applicants have invented a whole new prodrug methodology that is applicable to all sorts of M groups that are biologically active in some sort of phosphate, phosphonate, or phosphoramidate form. The numerous examples in the present specification show possession of at least a representative number of species of the claimed invention. Furthermore, the rest of the specification provides specific examples of many groups, suitable for M. For example, the portion of the specification labeled, Types of Parent Drugs, starting on page 41, line 6 and continuing to page 45, line 24 describes many parent drugs of the form MH, which are phosphorylated to become the biologically active drug, and of the form MPO_3^{2-}, $MP_2O_3^{3-}$, or $MP_3O_9^{4-}$.

As discussed in the referenced Written Description Guidelines:

> Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from

> other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

(See Section II.3a.(1)(b)(ii)) The present rejection is based, at least in part, on the Examiner's premise that the recited variable, M, is not defined in terms of its chemical structure. As is clear from the referenced Written Description Guidelines, however, disclosure of chemical structure is merely one factor to consider and is not conclusive on the issue of compliance with the written description requirement. In the present case, M is defined in terms of functional characteristics and biophysical properties. Nevertheless, the present invention, including the variable M, is also defined by at least partial chemical structure. Again, see the specification, starting on page 41. Applicants clearly had possession of the claimed subject matter at the time the application was filed. The subject matter of the rejected claims was described in such a way as to reasonably convey this fact to one skilled in the relevant art. Thus, withdrawal of this rejection is respectfully requested.

The Second Rejection

Claims 1-18, 20-46, 48-57, 150-157, and 165 stand rejected under 35 U.S.C. §112, First Paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is traversed.

Specifically, the Examiner contends that "[n]owhere in the specification are directions given for preparing the 'prodrugs' of the claimed compounds. Since the structures of these 'prodrugs' are uncertain, direction for their preparation must be even more unclear." (Office Action at p. 13) Applicants respectfully disagree with the Examiner's assertions.

First, prodrug is defined on page 15, line 7 of the specification, where it is taught that:

> The term 'prodrug' as used herein refers to any compound that when administered to a biological system generates a biologically active compound as a result of spontaneous chemical reaction(s) enzyme catalyzed reaction(s), and/or metabolic chemical reaction(s), or a combination of each. Standard prodrugs are formed using groups attached to functionality, *e.g.* HO-, HS-, HOOC-, R_2N-, associated with the drug, that cleave *in vivo*. Standard prodrugs include but are not limited to carboxylate esters where the group is alkyl, aryl, aralkyl, acyloxyalkyl, alkoxycarbonoxyalkyl as well as esters of hydroxyl, thiol and amines where the group attached is an acyl group, an alkoxycarbonyl, aminocarbonyl, phosphate or sulfate. The groups illustrated are exemplary not exhaustive, and one skilled in the art could prepare other known varieties of prodrugs. Such prodrugs of the compounds of formula I fall within the scope of the present invention.

It has been standard in the pharmaceutical arts for decades to make prodrugs as described in the specification. For example, the following references teach about prodrugs:

> Design of Biopharmaceutical Properties through Prodrugs and Analogs, ed. Edward B. Roche, American Pharmaceutical Association, Academy of Pharmaceutical Sciences, Washington, D.C., 1977.
> Design of Prodrugs, ed. H. Bundgaard, Elsevier Science Publishers B.V., Amsterdam, 1985.
> Higuchi, T., et al., "Prodrugs as Novel Drug Delivery Systems," ACS, Wa., 1975.
> *Comprehensive Medicinal Chemistry*, v.5, 1990, 122-133, 23.4.3, "Prodrugs."

Applicants are not required to teach that which is old in the art. The specification is enabling; it teaches that compounds of formula I may be substituted in such a way as to form prodrugs.

One skilled in the art, provided with the definition of prodrugs and the methods provided in the specification for preparation of compounds of formula I would understand the claimed structure and be able to prepare the claimed compounds and their prodrugs. As such, withdrawal of this rejection is respectfully requested.

The 35 U.S.C. §112, Second Paragraph, Rejections

The First Rejection

Claims 1-18 stand rejected under 35 U.S.C. §112, Second Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. This rejection is traversed.

Specifically, the Examiner contends that the phrase "fused to an aryl group at the beta and gamma position to the Y adjacent to V" is confusing." The Examiner also states: "[T]he word beta, when applied to rings indicates stereochemistry not position. . . . The word beta means up in steroids but down in carbohydrates. Since the cyclic group formed by V and Z is neither a steroid nor a carbohydrate, what do Applicants intend?" The Examiner also states: "The word gamma has no stereo chemical meaning in rings." Again, the Examiner asks what Applicants intend.

The definition of "together V and Z are connected via an additional 3 – 5 atoms to form a cyclic group, optionally containing one heteroatom, said cyclic group is fused to an aryl group attached at the beta and gamma position to the Y adjacent to V" is provided at page 16, line 16, to page 17, line 1, of the specification. The positions β and γ, as defined with regard to said definition, are clearly identified

in the structure at the top of page 17. Applicants respectfully disagree that such terms, as defined in the specification, are confusing to one skilled in the art and request that the rejection be withdrawn.

The Second Rejection

Claims 1-18, 20-46, 48-57, 150-157, and 165 stand rejected under 35 U.S.C. §112, Second Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. This rejection is respectfully traversed.

The Examiner refers to the fact that the terms: acyloxy, acyloxyalkyl, and lower acyl are recited in claim 1, but yet contends that the term "acyl" is indefinite. In questioning whether the term embraces the acids of sulfur and phosphorus, the Examiner states that the "accepted meaning of the term 'acyl' is 'any acid substituent with the OH group removed." The Examiner also poses a question as to how the acyl group is attached and what is the specific stem. Further, the Examiner wonders whether the adjective "lower" includes the carbonyl carbon atom in acyl groups derived from carboxylic acids.

The term acyl is defined on page 12, line 1, of the present specification, wherein it is stated: "The term 'acyl' refers to –C(O)R, where R is alkyl and aryl." Applicants are entitled to be their own lexicographer, as they have done in this case. Clearly, Applicants' definition of acyl does not embrace the acids of sulfur and phosphorus. Furthermore, consistent with the definition and use of "lower," throughout page 11, line 25, to page 14, line 25, of the specification, "lower" refers to the number of carbon atoms in R and does not include the carbonyl carbon (**C**) in –**C**(O)R. In view of this clarification, Applicants respectfully request that the rejection be withdrawn.

The Third Rejection

Claims 1-3, 7, 9-18, 20-46, 48-53, 150-157, and 165 stand rejected under 35 U.S.C. §112, Second Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. This rejection is respectfully traversed.

The Examiner contends that the phrase involving "M" on page 128, lines 16-17, recited in claim 1 is indefinite for three reasons. First, the Examiner asserts that it is unclear if M must itself contain phosphorus. Applicants respectfully disagree with the assertion that this claim language is unclear. Claim 1, on page 128, lines 16-18, recites that: "M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent . . . and is attached to the phosphorus in

formula I via a carbon, oxygen, sulfur or nitrogen atom." This recitation does not require nor suggest that M must contain a phosphorus. Indeed, it is clear that M in Formula I is attached to a phosphorus depicted in Formula I. The Examiner's confusion as to this issue is not understood.

Second, the Examiner questions what is intended by "biologically active agent." 'Biologically active drug or agent' is defined starting on page 21, line 32, of the specification and "refers to the chemical entity that produces the biological effect. In this invention, biologically active agents refers to $M\text{-}PO_3^{2-}$, $M\text{-}P(O\text{-})NHR^{6-}$, $MP_2O_6^{3-}$, or $MP_3O_9^{4-}$, where M can be the same M as in the parent drug or a metabolite." Given the teachings of the specification, Applicants believe that one skilled in the art is readily able to determine what is intended by the phrase "biologically active agent."

Third, the Examiner asks what is FBP or FBPase. The term FBPase is defined starting on page 5, line 18, of the specification to be: "fructose 1,6-bisphosphatase (FBPase)."

Applicants have particularly pointed out and distinctly claimed the subject matter that they regard as the invention, including the phrase describing M. In view thereof, Applicants respectfully request that the rejection be withdrawn.

The Fourth Rejection

Claims 1-3, 7, 9-18, 20-46, 48-53, 150-157, and 165 stand rejected under 35 U.S.C. §112, Second Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. This rejection is respectfully traversed.

The Examiner contends that "[t]he phrase in lines 20-21, page 128, "M is not –NH(lower alkyl, -N(lower alkyl)$_2$ is indefinite." (Office Action at p. 6) Specifically, the Examiner states, "M must be biologically active. Are NH_2(lower alkyl) or HN(lower alkyl)$_2$ biologically active? If not, the proviso excluded something that is not present. The nitrogen mustards excluded (lower alkyl halide) are toxins, thus meet the test of biologically active."

To be indefinite under 35 U.S.C. §112, second paragraph, one or ordinary skill in the art must not be able to tell what is inside or outside the scope of the claim. Regardless of the biological activity, the claim clearly and distinctly excludes these lower alkyl amines. There is no confusion.

Withdrawal of this rejection is requested, as Applicants have particularly pointed out and distinctly claimed the subject matter that Applicants regard as the invention.

The Fifth Rejection

Claims 1-18, 20-46, 48-57, 150-157, and 165 stand rejected under 35 U.S.C. §112, Second Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. This rejection is respectfully traversed.

Specifically, the Examiner refers to the term, "prodrug," in the phrase "and pharmaceutically acceptable prodrugs and salts thereof," but contends that prodrug is indefinite as used because the structures of the claimed compounds are not clearly defined. The Examiner argued that,

> Applicants' "prodrugs" are molecules whose structure lie outside the subject matter of claim 1, but upon metabolism in the body are converted to active compounds falling within the structural scope of claim 1. The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug". The compounds of formula (I) are described in the specification as prodrugs." Are Applicants are claiming prodrugs of prodrugs or does the word [prodrug] in line 23 simply reinforce the nature of the compounds of formula (I)?" (Office Action at page 7)

As discussed above under §112, First Paragraph, "prodrug" is defined on page 15, starting on line 7, of the specification:

> The term 'prodrug' as used herein refers to any compound that when administered to a biological system generates a biologically active compound as a result of spontaneous chemical reaction(s) enzyme catalyzed reaction(s), and/or metabolic chemical reaction(s), or a combination of each. Standard prodrugs are formed using groups attached to functionality, *e.g.* HO-, HS-, HOOC-, R_2N-, associated with the drug, that cleave *in vivo*. Standard prodrugs include but are not limited to carboxylate esters where the group is alkyl, aryl, aralkyl, acyloxyalkyl, alkoxycarbonoxyalkyl as well as esters of hydroxyl, thiol and amines where the group attached is an acyl group, an alkyxycarbonyl, aminocarbonyl, phosphate or sulfate. The groups illustrated are exemplary not exhaustive, and one skilled in the art could prepare other known varieties of prodrugs. Such prodrugs of the compounds of formula I fall within the scope of the present invention.

As defined by the present specification, the word "prodrug" recited in the rejected claims refers to prodrugs of the recited compounds of formula (I). In embodiments where compounds of formula (I) have, for example, a free amino group, the inclusion of the phrase "and pharmaceutically acceptable prodrugs and salts thereof" at the end of claim 1, makes it clear that prodrugs, such as an acylamino, of those compounds of formula (I) are also encompassed by the presently claimed invention. As discussed above, standard prodrug technology is well known in the art.

The Examiner's attention is drawn to MPEP §2173.01, where In re Swinehart, 439 F.2d 210, 160 USPQ 226 (CCPA 1971) is referenced: "[A] claim may not be rejected solely because of the type of language used to define the subject matter for which patent protection is sought." The absence of chemical structure for the recited term, "prodrug," is not, in and of itself, a proper basis for rejection under 35 U.S.C. §112, Second Paragraph. MPEP §2173.05(g), discussing functional limitations, references In re Barr, 444 F.2d 588, 170 USPQ 33 (CCPA 1971), where: "It was held that the limitation used to define a radical on a chemical compound as 'incapable of forming a dye with said oxidizing developing agent' although functional, was perfectly acceptable because it set definite boundaries on the patent protection sought." Similarly, MPEP §2173.05(t) states: "A claim to a chemical compound is not indefinite merely because a structure is not presented . . . ." Thus, Applicants contend that the requirements of 35 U.S.C. §112, Second Paragraph, are satisfied in the presently rejected claims. In view of the foregoing, withdrawal of this rejection is respectfully requested.

The Sixth Rejection

Claim 3 stands rejected under 35 U.S.C. §112, Second Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. This rejection is respectfully traversed.

Specifically, the Examiner inquires what is meant as to the recited "TS." The abbreviation TS is introduced on page 45, line 40, as follows: "thymidylate synthase (TS)." In view thereof, Applicants respectfully request that the rejection be withdrawn.

The Seventh Rejection

Claims 4-6, 8, 54, 55, and 57 stand rejected under 35 U.S.C. §112, Second Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. This rejection is respectfully traversed.

Specifically, the Examiner inquires as to the nature of the compounds whose abbreviations are recited. Based on the further discussion therein, it appears that the Examiner is specifically referring to the following terms: LdC, LdT, araA, AZT, PMEA, and TFT. All of these terms, which are recited in claims 4-6, 8, 54, 55, and 57, are defined in the specification, particularly in the list beginning on page 22. In view thereof, Applicants respectfully request that the rejection be withdrawn.

The Eighth Rejection

Claims 38, 42, 46, and 165 stand rejected under 35 U.S.C. §112, Second Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Specifically, the Examiner contends that the phrases "said prodrug" and "the prodrug" are indefinite and the nature of the structures being claimed is unclear. In light of the amendments made to claims 38, 42, 46 and 165 to more clearly recite "said compound," Applicants respectfully request that the rejection be withdrawn.

The Ninth Rejection

Claim 150 stands rejected under 35 U.S.C. §112, Second Paragraph, as allegedly indefinite. The Examiner argued,

> Claim 150 provides for transforming 'a compound drug having a $-PO_3^{2-}$...,' but since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. All the word "transforming" does is delineate which molecules are starting materials and which are products. What chemical reactions are being claimed? (Office Action at pg 9).

Method claims need only have one step. Claim 150 has a transforming step. The starting material is specified: $M\text{-}PO_3^{2-}$ or $MP(O)(NR^6)O^-$. The final product is specified: compounds of Formula I. Just because there is more than one way of "transforming" does not make the claim indefinite. For example, treatment claims often have a single "administering" step, yet they are not indefinite. One of ordinary skill in the art can understand the boundaries of the claim: transforming specified starting materials to compounds of Formula I. Thus the claim is not indefinite under 35 U.S.C. §112, Second Paragraph and Applicants respectfully request that the rejection be withdrawn.

The Tenth Rejection

Claims 154-157 stand rejected under 35 U.S.C. §112, Second Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. In the originally filed claims, claim 156 depended from claim 155, which depended from claim 154. Claim 154 has been cancelled and claim 166 has been added. Claim 155

now depends from independent claim 166. To facilitate prosecution of the newly pending claims, the Examiner's rejections to the original claims, as they survive in the newly filed claims, are addressed below.

Specifically, the Examiner contends that the recited phrase "oxidizing agent" (now in claim 166) is indefinite. After citing two different definitions for the terms "oxidizing agent" and "oxidizing material" from two different books, the Examiner inquires as to the structures of the reagents "whose use Applicants claim." Applicants contend that one skilled in the art, given the claimed transformation from a phosphoramidite to a compound of formula I would recognize a variety of appropriate oxidizing agents according to the present invention. The specification, at page 93, line 16 – 18, provides examples of appropriate oxidants, including molecular oxygen and t-butylhydroperoxide. Oxidizing agents according to the claimed invention are clearly those that transform the recited phosphoramidite into a compound of formula I. There is no ambiguity in this definition. In view thereof, Applicants respectfully request that the rejection be withdrawn.

The Eleventh Rejection

Claim 156 stands rejected under 35 U.S.C. §112, Second Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. In the originally filed claims, claim 156 depended from claim 155, which depended from claim 154. Claim 154 has been cancelled and claim 166 has been added. Claim 156 now ultimately depends from independent claim 166.

The Examiner contends that the phrase "using a chiral amino alcohol" is indefinite for two reasons. The first reason is the assertion that the claim did not set forth any steps involved in the method/process. Claim 156 depends from claim 155, which depends from claim 166. Claim 166 recites a method of making a prodrug comprising a converting step and a transforming step. Thus, dependent claim 156 comprises the method steps due to its claim dependency.

The second reason espoused for the rejection is that the Examiner is not sure what amino alcohol the phrase "a chiral amino alcohol" refers to. As recited in claim 156, a chiral amino alcohol is used to generate the chiral phosphoramidite recited in claim 155. As presented in the specification, page 92 line 10 to page 93 line 4, a chiral amino alcohol, HY-CH(V)CH(Z)CWW'-YH, can be used to generate the cyclic phosphoramidite. In particular, page 92, line 26 states "in the cases where unsymmetrical 1,3-

aminoalcohols...are used, the cyclic phosphoramidites are expected to form a mixture of chiral isomers."

In conclusion, it is believed that claim 156, as it presently reads, is definite. Withdrawal of this rejection is requested.

The 35 U.S.C. §101 Rejections

The First Rejection

Claim 150 stands rejected under 35 U.S.C. §101, as allegedly being an improper process claim. This rejection is respectfully traversed.

Specifically, the Examiner contends that the "recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process . . . ." In setting forth this rejection, the Examiner references Ex parte Dunki, 153 USPQ 678 (BPAI 1967). The reliance on this case is not understood. In Ex parte Dunki, the Board, in sustaining a rejection under 35 U.S.C. §103, held that the claims-at-issue need not necessarily be expressed in process form, but could be expressed in article form. Specifically, the Board stated: "Where the invention resides in the use of a particular material in a particular article, a properly expressed article claim is an appropriate definition of the invention." (Dunki at 679) The presently rejected claim, however, is not directed toward a use of a particular material in a particular article. In contrast, the presently rejected claim recites a "method of making a prodrug . . . ." The claimed method also includes step (a), a transforming step.

The Board in Ex parte Dunki and the Examiner also referred to Clinical Prod. Ltd. v. Brenner, 149 USPQ 475 (Dist. DC 1966), in stating that the word "use" does not describe a process, which would make it a statutory class of patentable subject matter under 35 U.S.C. §101. The claim-at-issue in Clinical Prod. Ltd. v. Brenner recited the "use as a sustained release therapeutic agent in the body of ephedrine adsorbed upon polystyrene sulphonic acid." In sustaining the Patent Office's rejection of this claim under 35 U.S.C. §101, the Court held that a "new 'use' of a known composition of matter can be properly claimed only by claiming the invention as a process or method." Again, the presently rejected claim is not directed toward a use, but rather to a "method of making a prodrug . . . ." Thus, Clinical Prod. Ltd. v. Brenner, as well as Ex parte Dunki, are not on point for the subject rejection.

Methods, such as the method recited in claim 150, are clearly within a statutory class of patentable subject matter. Applicants respectfully request that the rejection be withdrawn.

The Second Rejection

Claim 156 stands rejected under 35 U.S.C. §101, as allegedly being an improper process claim. In the originally filed claims, claim 156 depended from claim 155, which depended from claim 154. Claim 154 has been cancelled and claim 166 has been added. Claim 156 depends from claim 155, which depends from independent claim 166.

The Examiner contends that the "recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process . . . ." Claim 156 depends from claim 155, which depends from claim 166. Claim 166 recites two steps: a converting step and a transforming step. Thus, claim 156 does set forth steps involved in the claimed method due to its claim dependency and is a proper process claim. Applicants respectfully request that the rejection be withdrawn.

The 35 U.S.C. §102 Rejections

The First Rejection

Claims 1, 17, 18, 20, and 165 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Bentrude et al. ("Heterocycles Related to Cyclophosphamide. NMR, X-ray, and Infrared Studies of 2-Methoxy-2-oxo-1,3,2-oxazaphosphorinane and 2-Thio-1,3,2-oxazaphosphorinane," *J. Am. Chem. Soc.*, (1986) 108(21):6669-6675). This rejection is respectfully traversed.

Specifically, the Examiner contends that Compounds 8 and 10 disclosed by Bentrude et al. anticipate the presently claimed invention. Applicants respectfully disagree. In particular, the Examiner directs Applicants' attention to compounds where Z = tert-butyl and V = W = W' = hydrogen. However, proviso (b) in claim 1 of the present invention recites "when Z is R^2, then at least one of V, W and W' is not –H, alkyl, aralkyl, or alicyclic." (emphasis added)

Thus, Bentrude et al. do not teach or suggest each and every element of claim 1. Claims 17, 18, 20 and 165 ultimately depend from claim 1. As Bentrude et al. do not teach or suggest each and every limitation of the presently claimed invention, Applicants respectfully request that the rejection be withdrawn.

The Second Rejection

Claims 1, 9, 17, 18, 20, 150-152, 154-156, and 165 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Bentrude et al. ("Heterocycles. 2-aryl-1,3,2λ^5-oxazaphosphorinanes." *J. Am. Chem. Soc.*, (1988) 110(21):7119-7127). This rejection is respectfully traversed.

Specifically, the Examiner contends that Compounds 6, 8, 9, 11, and 12 disclosed by Bentrude et al. anticipate the presently claimed invention. Applicants respectfully disagree. In particular, the Examiner directs Applicants' attention to compounds where Z = tert-butyl and V = W = W' = hydrogen. However, proviso (b) in both independent claims 1 and 150 recites "when Z is R^2, then at least one of V, W and W' is not –H, alkyl, aralkyl, or alicyclic." (emphasis added)

Thus, Bentrude et al. do not teach or suggest each and every element of claims 1 and 150. Claims 9, 17, 18, 20, 151-152, 154-156 and 165 ultimately depend from one of these two independent claims. As Bentrude et al. do not teach or suggest each and every limitation of the presently claimed invention, Applicants respectfully request that the rejection be withdrawn.

The Third Rejection

Claims 1, 9, 17, 18, 20, 150-157, and 165 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Denmark et al. ("Asymmetric Electrophilic Amination of Chiral Phosphorus-Stabilized Anions," *Tetrahedron*, (1992) 48(11):2191-2208). This rejection is respectfully traversed.

Specifically, the Examiner contends that compound 1d disclosed in Tables 1 and 3, on pages 2193 and 2197, respectively, and the related synthesis on pages 2202-2203 anticipate the presently claimed invention. Applicants respectfully disagree. In particular, the Examiner directs Applicants' attention to compounds where Z = W = W' = methyl and V = hydrogen. However, proviso (b) in both independent claims 1 and 150 recites "when Z is R^2, then at least one of V, W and W' is not –H, alkyl, aralkyl, or alicyclic." (emphasis added)

Thus, Denmark et al. do not teach or suggest each and every element of claims 1 and 150. Claims 9, 17, 18, 20, 151-157 and 165 ultimately depend from one of these two independent claims. As Denmark et al. do not teach or suggest each and every limitation of the presently claimed invention, Applicants respectfully request that the rejection be withdrawn.

The Fourth Rejection

Claims 1, 2, 4, 7, 11-13, 17, 18, 20, 21, 29, and 165 stand rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Lorey et al. ("A New Cyclic Phosphoramidate d4T Prodrug Approach *Cyclo*Amb-d4T-phosphoramidates," Nucleosides & Nucleotides, (1999) 18(4&5): 947-8). This rejection is respectfully traversed.

Specifically, the Examiner contends that the compound referenced in the Office Action anticipates the claimed invention. Applicants respectfully disagree. The structural component recited in claim 1 of the present invention, -Y-CH(V)-CH(Z)-C(W)(W')-Y-, includes hydrogen bound to the carbon atoms attached to V and Z. Lorey et al. do not teach or suggest such compounds. For example, the referenced structure of Lorey et al., in which V = Z = a fused benzo ring, does not teach or suggest the recited structural component, where hydrogen atoms are bound to the carbon atoms attached to each of V and Z.

Thus, Lorey et al. do not teach or suggest each and every element of claim 1. Claims 2, 4, 7, 11-13, 17, 18, 20, 21, 29, and 165 ultimately depend from claim 1. As Lorey et al. do not teach each and every limitation of the presently rejected claims, Applicants respectfully request that the rejection be withdrawn.

The Fifth Rejection

Claims 1, 9, 11, 17, 18, 20, and 165 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Kamikawaji (Japanese Patent Publication No. 62-195392). This rejection is respectfully traversed.

Specifically, the Examiner contends that six compounds disclosed by Kamikawaji anticipate the presently claimed invention. The Examiner references a particular compound disclosed in Tables 1-6 of Kamikawaji and states that the "reference teaches that these compounds are useful for circulation disorders." What was supplied with the latest Office Action, however, is a Japanese-language version of the subject publication. It is not clear, from looking at the publication supplied, where the Examiner contends that the reference teaches that the compounds are useful for circulation disorders.

Consideration of the referenced compound, however, shows that it does not teach or suggest each and every limitation of claim 1. For example, proviso (b) in claim 1 recites "when Z is R^2, then at least one of V, W and W' is not –H, alkyl, aralkyl, or alicyclic." (emphasis added) In contrast, the compound

referenced by the Examiner, in which Z = R^2, W' = –H, and V = W = $–CH_3$ (*i.e.* alkyl), is excluded by this proviso.

Thus, Kamikawaji does not teach or suggest each and every limitation of claim 1. Claims 9, 11, 17, 18, 20, and 165 ultimately depend from claim 1. As Kamikawaji does not teach or suggest each and every limitation of the presently claimed invention, Applicants respectfully request that the rejection be withdrawn.

The Sixth Rejection

Claims 1, 2, 4, 7, 11-13, 17, 18, 20, 21, 29, and 165 stand rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Yoshikawa (Japanese Patent Publication No. 62-249996). This rejection is respectfully traversed.

Specifically, the Examiner contends that Compounds 81-87 and 100-102 of Yoshikawa anticipate the presently claimed invention. Applicants respectfully disagree. The structural component recited in claim 1 of the present invention, -Y-CH(V)-CH(Z)-C(W)(W')-Y-, includes hydrogen bound to the carbon atoms attached to V and Z. Yoshikawa does not teach or suggest such compounds. For example, the referenced compounds of Yoshikawa, in which V = Z = a fused benzo ring, do not teach or suggest the recited structural component, where hydrogen atoms are bound to the carbon atoms attached to each of V and Z.

Thus, Yoshikawa does not teach or suggest each and every element of claim 1. Claims 2, 4, 7, 11-13, 17, 18, 20, 21, 29, and 165 ultimately depend from claim 1. As Yoshikawa does not teach each and every limitation of the presently rejected claims, Applicants respectfully request that the rejection be withdrawn.

The Seventh Rejection

Claims 1, 2, 9, 11, 12, 13, 17, 18, 20, and 165 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Akiyama et al. (U.S. Patent No. 5,130,303). This rejection is respectfully traversed.

Specifically, the Examiner contends that the second compound in the table in Col. 23 of Akiyama et al., as well as the compounds of claims 3 and 4, anticipate the presently claimed invention. Applicants respectfully disagree. In particular, the Examiner directs Applicants' attention to compounds

where V = W = methyl and Z = W' = hydrogen. If the Examiner is aware of any other compounds taught by Akiyama et al. that are potentially related to the presently claimed invention, the Examiner is requested to notify Applicants of the same. In this case, however, proviso (b) in claim 1 recites "when Z is R^2, then at least one of V, W and W' is not –H, alkyl, aralkyl, or alicyclic." (emphasis added)

Thus, Akiyama et al. do not teach or suggest each and every limitation of claim 1. Claims 2, 9, 11, 12, 13, 17, 18, 20, and 165 ultimately depend from claim 1. As Akiyama et al. do not teach each and every limitation of the presently claimed invention, Applicants respectfully request that the rejection be withdrawn.

Conclusion

In conclusion, Applicants respectfully submit that all pending claims are in condition for allowance. The Examiner is invited to contact Applicants' undersigned Representative if it is believed that prosecution may be furthered thereby.

Respectfully Submitted,

Erion et al.

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MARKED UP COPY OF AMENDED PARAGRAPHS OF SPECIFICATION

Please replace the paragraph on page 2, lines 13-15, with the following:

--Cyclic [3',5'-phosphate] 3',5'-phosphate esters of araA, araC and thioinosine have been synthesized. [Meier] Meyer *et al., J. Med. Chem.* 22: 811-815 (**1979**). These compounds are ring-opened through the action of phosphodiesterases, which usually require one negative charge.--

Please replace the paragraph on page 4, lines 1-21, with the following:

--A variety of substituted [1',3' propanyl] 1',3'-propanyl cyclic phosphoramidates, wherein [1'] 1' represents the carbon alpha to the nitrogen, were prepared as cyclophosphamide analogs (Zon, [Progress in Med. Chem.] *Progress in Med. Chem.*, 19, [1205] 205 (1982)). For example, a number of [2'-] 2'- and [3'-] 3'-substituted proesters were prepared in order to decrease the propensity of the α,β-unsubstituted carbonyl by-product to undergo a Michael reaction. [2'-Substituents] 2'-substituents included methyl, dimethyl, bromo, trifluoromethyl, chloro, hydroxy, and methoxy, whereas a variety of groups were used at the [3'-position] 3'-position, including phenyl, methyl, trifluoromethyl, ethyl, propyl, i-propyl, and cyclohexyl. Analogs with a [3'-aryl] 3'-aryl group (*e.g.* trans-4-phenylcyclophosphamide) were "moderately effective in L1210- test system and showed no activity *in vivo*." G. [Zu] Zon, [Prog. Med. Chem.,] *Prog. Med. Chem.*, *19*: 205-246 (1982). A variety of [1'-substituted] 1'-substituted analogs were also prepared. In general, these compounds were designed to be "pre-activated" cyclophosphamide analogs that bypass the oxidation step by already existing as a [1'-substituted] 1'-substituted analog capable of producing the final compound, *e.g.* hydroperoxide and 1-thioether. A series of [1'-aryl] 1'-aryl analogs were also prepared in order to enhance the oxidation potential. In contrast to the [1'-hydroperoxy] 1'-hydroperoxy analogs, the [1'-aryl] 1'-aryl compounds exhibited either no activity or very poor activity in the standard anticancer *in vivo* screen assay, *i.e.* the mouse L1210 assay. The lack of activity was postulated to arise from the steric hindrance of the phenyl and, therefore, limited oxidation of the prodrug. Support for this postulate was the potent activity of the acyclic phenyl keto analog, which exhibited activity similar to cyclophosphamide. [Luderman] Ludeman et al., [J. Med. Chem.] *J. Med. Chem.* *29*: 716 (1986).--

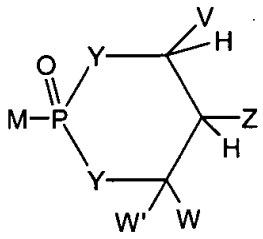
Please replace the paragraph on page 27, lines 7-16, with the following:

--The most common prodrug class, and the class almost exclusively used for clinical candidates, is the acyloxyalkyl esters. These prodrugs, however, often exhibit only a modest improvement in oral bioavailability due to poor aqueous stability, poor stability to acidic/basic pH and rapid degradation by esterases in the gastrointestinal tract (Shaw & Cundy, *Pharm. Res.* **10**, (Suppl), S294 (1993)). Another class of prodrugs are the bis-aryl prodrugs (e.g. [DeLombert] DeLombaert et al., [J. Med. Chem.] *J. Med. Chem.*, 37, 498 (1994)), which have shown in a few isolated cases to provide good to modest improvements in oral bioavailability. The major limitation with this class of compounds is that the prodrug ester often is degraded to the monoacid rapidly *in vivo,* but conversion to the parent drug occurs only slowly (sometimes over days) if at all.--

MARKED UP VERSION OF AMENDED CLAIMS

Please amend the indicated claims to read as follows:

1. (Once amended) A compound of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of –CHR^2OH , -$CHR^2OC(O)R^3$, -$CHR^2OC(S)R^3$, -$CHR^2OC(S)OR^3$, -$CHR^2OC(O)SR^3$, -$CHR^2OCO_2R^3$, -OR^2 , -SR^2, -CHR^2N_3, -CH_2aryl, -CH(aryl)OH, -$CH(CH=CR^2_2)OH$, -$CH(C\equiv CR^2)OH$, -R^2 , -NR^2_2, -$OCOR^3$, -OCO_2R^3, -$SCOR^3$, -SCO_2R^3, -$NHCOR^2$, -$NHCO_2R^3$, -CH_2NHaryl, -$(CH_2)_p$-OR^{12}, and -$(CH_2)_p$-SR^{12};

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is -R^2, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, -NR^6- with the proviso that at least] one <u>Y is –O- and the other</u> Y is -NR^6-;

M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

1) M is not –NH(lower alkyl), -N(lower alkyl)$_2$, -NH(lower alkylhalide), –N(lower alkylhalide)$_2$, or –N(lower alkyl) (lower alkylhalide); and

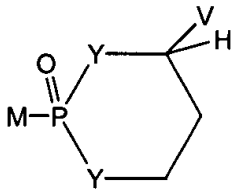
2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

2. (Once amended) The compounds of claim 1 wherein $MP(O)(NHR^6)O^-$, MPO_3^{2-}, $MP_2O_6^{3-}$, [and] <u>or</u> $MP_3O_9^{4-}$ is selected from the group consisting of an antiviral, anticancer, antihyperlipidemic, antifibrotic, and antiparasitic agent[s].

3. (Once amended) The compound of claim 1 wherein $MP(O)(NHR^6)O^-$, MPO_3^{2-}, $MP_2O_6^{3-}$, [and] or $MP_3O_9^{4-}$ is selected from the group consisting of metalloprotease inhibitor[,] and TS inhibitor.

38. (Once amended) The compounds of claim 20 wherein said [prodrug is a] compound is of formula VI:

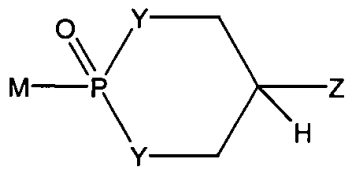


VI

wherein

V is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

42. (Once amended) The compounds of claim 20 wherein said [prodrug is a] compound is of formula VII:

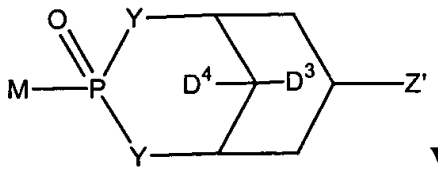


VII

wherein

Z is selected from the group consisting of:
$-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OC(S)OR^3$, and $-CH_2$aryl.

46. (Once amended) The compounds of claim 20 wherein said [prodrug is a] compound is of formula VIII:



VIII

wherein

Z' is selected from the group consisting of -OH, $-OC(O)R^3$, $-OCO_2 R^3$, and $-OC(O)S R^3$;

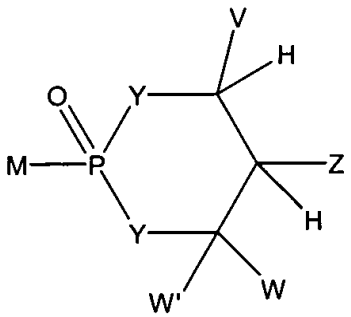
D^3 is –H;

D^4 is selected from the group consisting of -H, alkyl, -OH, and $-OC(O)R^3$.

48. (Once amended) The compounds of claim 32 wherein W and W' are H, V is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl, and Z is selected from the group consisting of -H, OR^2, and $-NHCOR^2$.

50. (Once amended) The compounds of claim 49 wherein V is selected from the group consisting of phenyl [or] and substituted phenyl.

58. (Once amended) A method of enhancing oral bioavailability of a parent drug by administering to an animal a [prodrug] compound of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, $-NR^6-$ with the proviso that at least] one Y is –O- and the other Y is $-NR^6-$;

M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$, or $P(O)(NHR^6)O^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

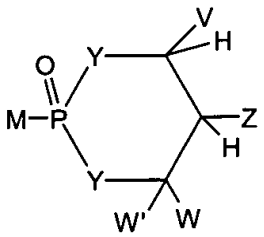
1) M is not –NH(lower alkyl), -N(lower alkyl)$_2$, -NH(lower alkylhalide), –N(lower alkylhalide)$_2$, or –N(lower alkyl) (lower alkylhalide); and

2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

64. (Once amended) The method[s] of claim 63 wherein MPO_3^{2-}, $MP_2O_6^{3-}$, or $MP_3O_9^{4-}$ is an antiviral or anticancer agent.

70. (Once amended) A method of delivering a biologically active drug to an animal for a sustained period [using] by administering to an animal a compound[s] of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and

1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, $-NR^6-$ with the proviso that at least] one Y is –O- and the other Y is $-NR^6-$;

M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

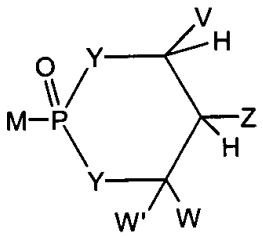
with the provisos that:

1) M is not –NH(lower alkyl), -N(lower alkyl)$_2$, -NH(lower alkylhalide), –N(lower alkylhalide)$_2$, or –N(lower alkyl) (lower alkylhalide); and

2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

75. (Once amended) A method of delivering a biologically active drug to an animal with greater selectivity for the liver [using] by administering to an animal a compound[s] of formula I:



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wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, $-NR^6-$ with the proviso that at least] one Y is –O- and the other Y is $-NR^6-$;

M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

1) M is not –NH(lower alkyl), -N(lower alkyl)$_2$, -NH(lower alkylhalide), –N(lower alkylhalide)$_2$, or –N(lower alkyl) (lower alkylhalide); and

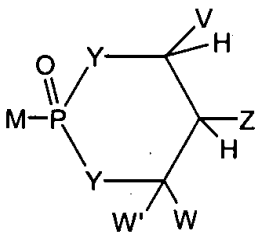
2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

81. (Once amended) The method of claim 80 wherein [the] said biologically active drug is [selected from the group consisting of] FdUMP.

83. (Once amended) The method of claim 82 wherein the parent drug MPO_3^{2-} is selected from the group consisting of PMEA; PMEDAP; HPMPC, HPMPA; FPMEA; PMPA foscarnet, and phosphoracetic acid.

84. (Once amended) A method of increasing the therapeutic index of a drug by administering to an animal a compound[s] of formula I:



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wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, -NR^6- with the proviso that at least] one Y is –O- and the other Y is -NR^6-;

M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

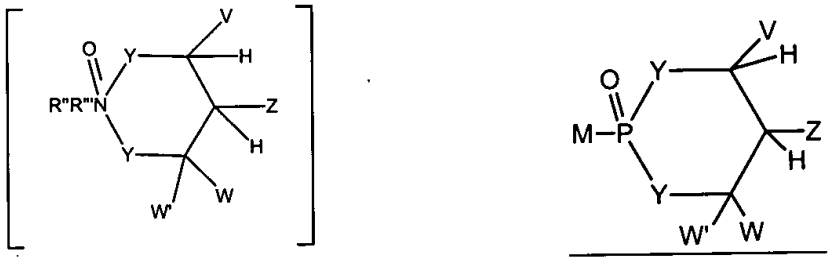
with the provisos that:

1) M is not –NH(lower alkyl), -N(lower alkyl)$_2$, -NH(lower alkylhalide), –N(lower alkylhalide)$_2$, or –N(lower alkyl) (lower alkylhalide); and

2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

89. (Once amended) A method of bypassing kinase resistance by administering to an animal a compound[s] of formula I:



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wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, $-NR^6-$ with the proviso that at least] one Y is –O- and the other Y is $-NR^6-$;

M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

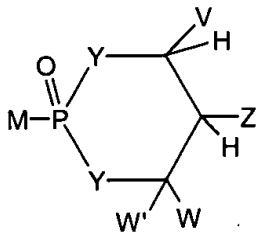
1) M is not –NH(lower alkyl), -N(lower alkyl)$_2$, -NH(lower alkylhalide), –N(lower alkylhalide)$_2$, or –N(lower alkyl) (lower alkylhalide); and

2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

93. (Once amended) The method of claim 92 wherein MH is selected from the group consisting of F-ara-A, araC, CdA, dFdc, and 5-fluoro-2'-deoxyuridine.

97. (Once amended) A method of treating cancer expressing a P450 enzyme, by administering to an animal a compound of formula I:



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wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, $-NR^6-$ with the proviso that at least] one Y is –O- and the other Y is $-NR^6-$;

M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

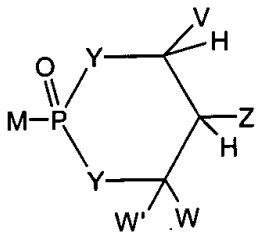
1) M is not –NH(lower alkyl), -N(lower alkyl)$_2$, -NH(lower alkylhalide), –N(lower alkylhalide)$_2$, or –N(lower alkyl) (lower alkylhalide); and

2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

101. (Once amended) The method of claim 97 wherein said [prodrug] compound is administered to patients resistant to the parent drug.

106. (Once amended) A method of treating liver fibrosis by administering to an animal a compound of formula I:



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wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, $-NR^6-$ with the proviso that at least] one Y is –O- and the other Y is $-NR^6-$;

M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

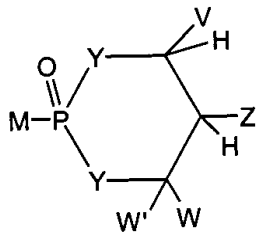
with the provisos that:

1) M is not –NH(lower alkyl), -N(lower alkyl)$_2$, -NH(lower alkylhalide), –N(lower alkylhalide)$_2$, or –N(lower alkyl) (lower alkylhalide); and

2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

107. (Once amended) A method of treating hyperlipidemia by administering to an animal a compound of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, $-NR^6-$ with the proviso that at least] one Y is –O- and the other Y is $-NR^6-$;

M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

1) M is not –NH(lower alkyl), -N(lower alkyl)$_2$, -NH(lower alkylhalide),

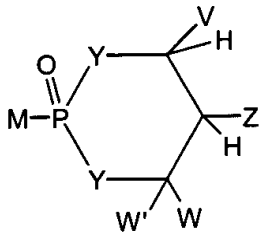
–N(lower alkylhalide)$_2$, or –N(lower alkyl) (lower alkylhalide); and

2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

108. (Once amended) The method of claim 107 wherein [the hyperlipidemia agent] $\underline{MPO_3^{2-}}$, $\underline{MP_2O_6^{3-}}$, $\underline{MP_3O_9^{4-}}$ or $\underline{MP(O)(NHR^6)O^-}$ is a squalene synthase inhibitor.

109. (Once amended) A method of treating a parasitic infection[s] by administering to an animal a compound of formula I:



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wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and

aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, $-NR^6-$ with the proviso that at least] one Y is –O- and the other Y is $-NR^6-$;

M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

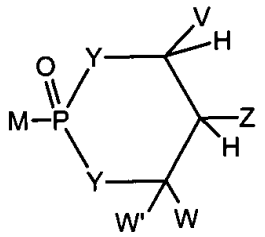
with the provisos that:

1) M is not –NH(lower alkyl), -N(lower alkyl)$_2$, -NH(lower alkylhalide), –N(lower alkylhalide)$_2$, or –N(lower alkyl) (lower alkylhalide); and

2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

110. (Once amended) A method of delivering a diagnostic imaging agent[s] to the liver comprising [administration] administering to an animal [of] a compound of formula I:



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wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$,

$-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2{}_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2{}_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, $-NR^6-$ with the proviso that at least] one Y is –O- and the other Y is $-NR^6-$;

M is selected from the group that attached to $PO_3{}^{2-}$, $P_2O_6{}^{3-}$, $P_3O_9{}^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

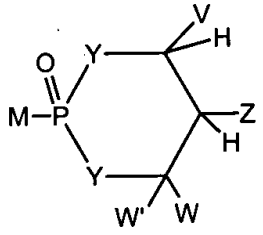
with the provisos that:

1) M is not –NH(lower alkyl), $-N(\text{lower alkyl})_2$, -NH(lower alkylhalide), $-N(\text{lower alkylhalide})_2$, or –N(lower alkyl) (lower alkylhalide); and

2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

112. (Once amended) A method of treating a viral infection[s] by administering to an animal a compound of formula I:



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wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, $-NR^6-$ with the proviso that at least] one Y is –O- and the other Y is $-NR^6-$;

M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

1) M is not –NH(lower alkyl), -N(lower alkyl)$_2$, -NH(lower alkylhalide), –N(lower alkylhalide)$_2$, or –N(lower alkyl) (lower alkylhalide); and

2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

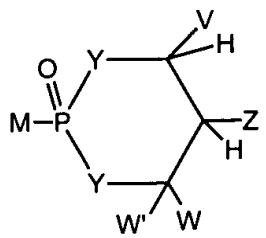
115. (Once amended) The method of claim 113 wherein said [prodrug] compound is administered to patients resistant to the parent drug.

118. (Once amended) The method[s] of claim 112 wherein viral kinases produce M-PO_3^{2-}.

121. (Once amended) A method of delivering a biologically active drug to target tissues comprising:

a) enhancing the activity of a P450 enzyme that oxidizes the compounds of formula I in said target tissues; and

b) administering to an animal a compound of formula I:



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wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, -NR^6- with the proviso that at least] one Y is –O- and the other Y is -NR^6-;

M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$, or $P(O)(NHR^6)O^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

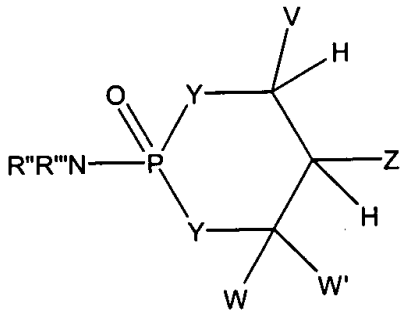
1) M is not –NH(lower alkyl), -N(lower alkyl)$_2$, -NH(lower alkylhalide), –N(lower alkylhalide)$_2$, or –N(lower alkyl) (lower alkylhalide); and

2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

124. (Once amended) The method of claim 121 wherein said P450 enzyme activity is enhanced by administration of a compound that increases the amount of [engodenous] endogenous P450 enzyme.

126. (Once amended) A method of treating tumor cells expressing a P450 enzyme comprising administering a cyclophosphamide analog selected from the group consisting of



wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{66} is selected from the group consisting of -H, lower 2-haloalkyl, and lower alkyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

R" is lower 2-haloalkyl;

R"' is selected from the group consisting of H, lower alkyl, and R";

[each Y is independently selected from the group consisting of -O-, -NR^{66}- with the proviso that at least] one Y is –O- and the other Y is -NR^{66}-;

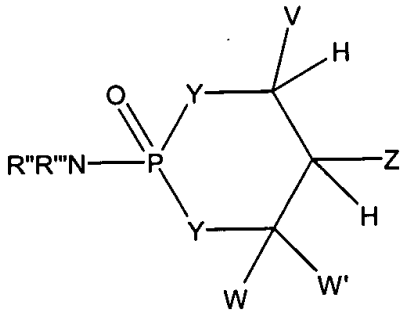
and pharmaceutically acceptable prodrugs and salts thereof.

131. (Once amended) The method of claim 127 wherein the activity of a P450 enzyme is enhanced by administration of a compound that increases the amount of [engodenous] endogenous P450 enzyme.

138. (Once amended) A method of treating tumor cells comprising

a) enhancing the activity of a P450 enzyme that oxidizes cyclophosphamide analogs;

b) administering to an animal a cyclophosphamide analog selected from the group consisting of:



wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{66} is selected from the group consisting of -H, lower 2-haloalkyl, and lower alkyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

R" is lower 2-haloalkyl;

R''' is selected from the group consisting of H, lower alkyl, and R";

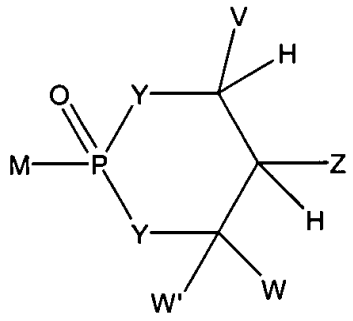
[each Y is independently selected from the group consisting of -O-, -NR^{66}- with the proviso that at least] one Y is –O- and the other Y is -NR^{66}-;

and pharmaceutically acceptable prodrugs and salts thereof.

141. (Once amended) The method of claim 138 wherein said P450 enzyme activity is enhanced by administration of a compound that increases the amount of [engodenous] endogenous P450 enzyme.

150. (Once amended) A method of making a [prodrug of a] compound of Formula I [drug having a -PO_3^{2-} or -P(O)(NHR^6)O^- moiety] comprising,

a) transforming [said phosph(on)ate] a drug having a -PO_3^{2-} or -P(O)(NHR^6)O^- moiety into a compound of formula I:



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wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, $-NR^6-$ with the proviso that at least] one Y is –O- and the other Y is $-NR^6-$;

M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$, or $P(O)(NHR^6)O^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

1) M is not –NH(lower alkyl), -N(lower alkyl)$_2$, -NH(lower alkylhalide), –N(lower alkylhalide)$_2$, or –N(lower alkyl) (lower alkylhalide); and

2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

151. (Once amended) The method of claim 150 further comprising,

a) converting M-PO_3^{2-} to a compound M-P(O)L"$_2$ wherein L" is a halogen [leaving group selected from the group consisting of halogen]; and

b) reacting M-P(O)L"$_2$ with [HY-CH(V)CH(Z)CH(Z)-CW(W')-YH.] HY-CH(V)CH(Z)-CW(W')-YH.

155. (Once amended) The method of claim [154] 166 wherein L-P(-YCH(V)CH(Z)-CW(W')Y-) is chiral.

161. (Once amended) A compound, R^1_2N-P-(-YCH(V)CH(Z)-CW(W')Y-) wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

each R^1 is independently selected from the group consisting of alkyl, aryl, and aralkyl or together R^1 and R^1 form a cyclic group, optionally containing a heteroatom;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

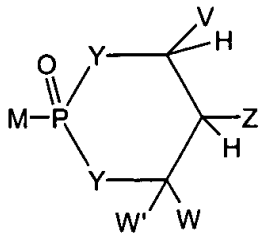
R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, $-NR^6-$ with the proviso that at least] one <u>Y is –O- and the other</u> Y is $-NR^6-$;

with the proviso that R^1 is not methyl.

163. (Once amended) A method of delivering a compound to hepatocytes wherein said compound has a moiety selected from the group consisting of phosph(on)ate comprising:

a) converting said compound to a [prodrug] compound of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of –CHR^2OH , -$CHR^2OC(O)R^3$, -$CHR^2OC(S)R^3$, -$CHR^2OC(S)OR^3$, -$CHR^2OC(O)SR^3$, -$CHR^2OCO_2R^3$, -OR^2 , -SR^2, -CHR^2N_3, -CH_2aryl, -CH(aryl)OH, -$CH(CH=CR^2_2)OH$, -$CH(C\equiv CR^2)OH$, -R^2 , -NR^2_2, -$OCOR^3$, -OCO_2R^3, -$SCOR^3$, -SCO_2R^3, -$NHCOR^2$, -$NHCO_2R^3$, -CH_2NHaryl, -$(CH_2)_p$-OR^{12}, and -$(CH_2)_p$-SR^{12};

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is -R^2, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, -NR^6- with the proviso that at least] one <u>Y is –O- and the other</u> Y is -NR^6-;

M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

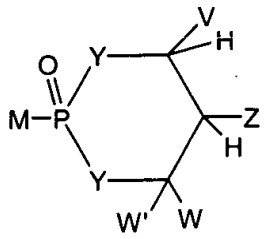
with the provisos that:

1) M is not –NH(lower alkyl), -N(lower alkyl)$_2$, -NH(lower alkylhalide), –N(lower alkylhalide)$_2$, or –N(lower alkyl) (lower alkylhalide); and

2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

164. (Once amended) A method of enhancing the pharmacodynamic half-life of a parent drug by administering to an animal a [prodrug] <u>compound</u> of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$,

$-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NHaryl$, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

[each Y is independently selected from the group consisting of -O-, $-NR^6-$ with the proviso that at least] one Y is –O- and the other Y is $-NR^6-$;

M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

1) M is not –NH(lower alkyl), -N(lower alkyl)$_2$, -NH(lower alkylhalide), –N(lower alkylhalide)$_2$, or –N(lower alkyl) (lower alkylhalide); and

2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

165. (Once amended) The compounds of claim 1 wherein V and M are *cis* to one another on the phosphorus-containing ring of Formula I [the prodrug].